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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,586	08/13/1999	DAVID J. PINSKY	59167/JPW/JM	3944

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EXAMINER

CHEN, SHIN LIN

ART UNIT

PAPER NUMBER

1633

DATE MAILED: 01/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/374,586

Applicant(s)

PINSKY, DAVID J.

Examin r

Shin-Lin Chen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 October 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 16-26 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 and 16-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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DETAILED ACTION

Continued Prosecution Application

1. The request filed on 12-20-01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/374,586 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's preliminary amendment filed 12-7-01 has been entered. Claims 1, 2, 9-11 and 17 have been amended. Claims 1-13 and 16-26 are pending and under consideration.

Claim Objections

Claim 17 is objected because the claim recites "and/or" in line 15 under section (d). Changing "and/or" to "or" and adding "or both" after the phrase "fibrin deposition" in line 15 would be remedial.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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3. Claims 2 , 4, 5, 8 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term “mutated” in claim 2 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered “mutated”? If the term “mutated” means substitution, addition, or deletion of amino acids within SEQ ID No. 1, then claim 2 fails to provide further limitation from claim 1. Claim 1 encompasses polypeptide that comprises active polypeptide fragment of SEQ ID No. 1 and therefore does not encompass substitution, deletion other than truncation, or addition of amino acids within SEQ ID NO. 1.

The phrase “having IL-2 as its leader sequence” in claim 4 is vague and renders the claim indefinite. IL-2 is a cytokine that has a leader sequence. It is unclear how one would use the whole IL-2 as a leader sequence. Claim 5 depends on claim 4 but fails to clarify the indefiniteness.

The phrase “the CD39 polypeptide or its fragment is **linked** to a pharmaceutical acceptable carrier” in claim 8 is vague and renders the claim indefinite. It is unclear how the CD39 polypeptide or its fragment is going to **link** to a pharmaceutical acceptable carrier. The specification fails to define the linking of a CD39 polypeptide or its fragment to a pharmaceutical acceptable carrier. Claim 16 depends on claim 8 but fails to clarify the indefiniteness.

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4. Claims 17-26 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MEP. § 2172.01. The omitted steps are: Step (e) of claim 17 fails to specifically points out the condition that would indicates the compound is capable of treating or preventing thrombotic or ischemic disorders in a subject, such as decrease of platelet deposition would indicate the compound can inhibit platelet aggregation and is capable of treating or preventing thrombotic or ischemic disorders.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2, 6, 7, 21 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2, 6 and 7 read on using mutated form of CD39 polypeptide, or a polypeptide comprising amino acid position 1-50 of SEQ ID No. 2 or comprising 20-80 amino acid residues of SEQ ID No. 1 that mimic the active site, to treat or prevent stroke in a human subject susceptible to intracranial hemorrhaging.

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The specification discloses that SEQ ID No. 1 is the coding sequence of CD39 and SEQ ID No. 2 is a variant of CD39 (specification, page 9, lines 3-5). The specification provides general disclosure on the composition of other variants, such as that they have substitutions, deletions, or insertions which do not abolish the biological activity associated with CD39 and which may have increased potency, bioavailability, stability or decreased toxicity (specification, page 9, line 28-page 12, line 10). In the various exemplifications provided in the specification, only the polypeptide of SEQ ID No. 2 is utilized (soluble CD39 lacking C-terminal and N-terminal transmembrane domains).

The scope of the claims encompass a genus of structural variants of SEQ ID No. 1 and the genus is highly variant because a significant number of structural differences between genus members is permitted. A polypeptide comprising a mutated form of SEQ ID No. 1 via substitution, deletion or addition, or an active fragment comprising amino acid position 1-50 of SEQ ID No. 2 or comprising 20-80 amino acid residues of SEQ ID No. 1 encompass numerous unknown and unidentified polypeptide sequences that differ dramatically from the polypeptide sequence of SEQ ID No. 1. The structural features that could distinguish CD39 fragments, having activity in inhibiting adenosine diphosphate (ADP)-mediated platelet aggregation by increasing ADP catabolism, in the genus from others in the polypeptide class are missing from the disclosure. The specification fails to disclose the active site of CD39 that contribute to its activity in inhibiting ADP-mediated platelet aggregation by increasing ADP catabolism. No common structural attributes identify the members of the genus. The general knowledge and

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level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of SEQ ID No. 1 and 2 is insufficient to describe the genus. This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the numerous variants of SEQ ID No. 1 as claimed in the present invention. Thus it is concluded that the written description requirement is not satisfied for the genus.

Claims 21 and 25 are directed to a compound identified by the method of claim 17, and a pharmaceutical composition comprising said compound and a pharmaceutical acceptable carrier. The claims encompass a genus of organic compounds that could be identified via the method of claim 17, which reads on far more than compounds structurally and functionally related to CD39.

The specification only discloses that SEQ ID No. 1 is the coding sequence of CD39 and SEQ ID No. 2 is a variant of CD39 (specification, page 9, lines 3-5). Organic compound and polypeptide, such as CD39, have different physical and chemical properties and they also differ in their functional characteristics. The specification fails to disclose the physical and chemical properties of the claimed compound and what functional characteristics of an organic compound would inhibit platelet aggregation or leucocyte accumulation by increasing ADP catabolism and not increase incidence of intracerebral hemorrhage. The structural feature of a compound that would inhibit platelet aggregation or leucocyte accumulation by increasing ADP catabolism was not disclosed. One skilled in the art at the time of the invention would not be able to distinguish

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the compound having the ability in inhibiting platelet aggregation from the compound that does not have such ability based solely on the description in the specification of such compound, i.e. the specification discloses no structural features of such compounds. The specification fails to provide sufficient description of the claimed compounds that could be identified by claim 17. The limited information of SEQ ID Nos. 1 and 2 is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the genus of compounds or compositions comprising said compounds as claimed in the present invention. Thus it is concluded that the written description requirement is not satisfied for the genus.

7. Claims 2, 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of soluble CD39 in the treatment and prevention of thrombotic and ischemic disorders in mice and BIBU52 in rhesus and marmoset monkeys (Guth et al., abstract), does not reasonably provide enablement for the use of any mutated CD39 fragment, an active fragment comprising amino acid position 1 to 50 of SEQ ID No. 2 or an active fragment comprising about 20-80 amino acid residues of SEQ ID No. 1 in treating or preventing stroke. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 2, 6 and 7 read on using mutated form of CD39 polypeptide, or a polypeptide comprising amino acid position 1-50 of SEQ ID No. 2 or comprising 20-80 amino acid residues

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of SEQ ID No. 1, to treat or prevent stroke in a human subject susceptible to intracranial hemorrhaging.

As stated in the preceding section, the specification fails to disclose the identity of any CD39 variant, other than the exemplified SEQ ID No. 2, with the ability to inhibit platelet aggregation by increasing ADP catabolism. Although the specification provides a general disclosure on the methods of generating additional CD39 variants (specification, p. 8, line 25-p. 12, line 10), said disclosure does not provide specific details on the structural feature of a fragment which is necessary to inhibit platelet aggregation. Further, The amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). One skilled in the art would not know how to make and use the claimed CD39 variants or polypeptide comprising amino acid position 1-50 of SEQ ID

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No. 2 or comprising 20-80 amino acid residues of SEQ ID No. 1 that have ability to inhibit platelet aggregation by increasing ADP catabolism.

Therefore, in the absence of teachings disclosing the ability of any variant other than the soluble form of CD39 (SEQ ID No. 2) to inhibit platelet aggregation or ADPase activity *in vivo*, or even to maintain its biological activity *in vivo* for long periods of time following i.v. administration (see Gayle et al., p. 1853, column 1), and the unpredictability of biological function of a polypeptide from mere amino acid sequence, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed.

8. Claims 17-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a homozygous deletion in CD39 and its use in identifying compounds which inhibit platelet aggregation via the ADP pathway, does not reasonably provide enablement for the use of an animal model in testing for compounds which inhibit platelet aggregation via any pathway other than ADP catabolism pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 17-26 are directed to a method for determining whether a compound inhibits platelet aggregation or leukocyte accumulation by increasing ADP catabolism and does not

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increase incidence of intracerebral hemorrhage by inducing thrombotic or ischemic disorders in an animal, administering a test compound to said animal and measuring platelet deposition and/or fibrin deposition in ischemic tissue in the animal, the compound identified by said method, and a composition containing said compound.

The specification fails to provide an enabling disclosure for the use of an animal model to test for compounds which inhibit platelet aggregation via pathways other than ADP catabolism by measuring said compound effect on all types of platelet deposition. Platelet aggregation during thrombosis is included by collagen, ADP, and a thrombin receptor-activating peptide (Guth et al., abstract). The soluble CD39 has been disclosed by the art to be an ADPase, the claimed invention is not enabled for testing compounds which are not previously known to be ADPase's because one skilled in the art at the time of the invention would not be able to discern if any platelet aggregation resulting from use of a test compound acted via collagen or thrombin receptor-activating peptide pathway or ADPase pathway. The specification fails to teach the manner of blocking the collagen or thrombin receptor-activating pathways in the animal model to ensure that any effect the compound had on the inhibition of platelet aggregation was through the ADPase catabolism pathway as regarded by the claims. The specification also fails to disclose assays to test specifically for inhibition of platelet aggregation via the ADPase pathway versus via the inhibition of the collagen or thrombin receptor-activating pathways. Therefore, one of skilled in the art at the time of the invention would be required to engage in undue experimentation to identify the pathway by which any compound might inhibit platelet

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aggregation in the claimed animal model or to amend the method to add steps that would discriminate between compounds acting on ADP catabolism and those acting on other pathways that inhibit platelet and fibrin depositions.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 21, 25 and 26 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Gayle et al., 1998 (The Journal Clinical Investigation, Vol. 10, No. 9, p. 1851-1859, exhibit G).

Claims 21, 25 and 26 are directed to a compound identified by the method of claim 17, a pharmaceutical composition comprising said compound, and a pharmaceutical composition comprising a CD39 polypeptide or an active fragment thereof and a pharmaceutical acceptable carrier.

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Gayle discloses preparation of a recombinant soluble form of CD39 by affinity purification and demonstrate its antithrombotic activity *in vitro* by catabolizing ADP and resulting in the inhibition of platelet aggregation, and that it remained biologically active *in vivo* while circulating for prolonged periods of time (e.g. abstract, Figure 1, p. 1852, 1858). Claims 21, 25 and 26 are composition claims. The method by which the composition is obtained does not carry weight in 35 U.S.C. 102 rejection. The soluble form of CD39 can inhibit platelet aggregation. The solution containing the soluble form of CD39 is a pharmaceutical acceptable carrier. Thus, claims 21, 25 and 26 are clearly anticipated by Gayle.

11. Claims 21 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Guth et al., 1997 (Journal of Cardiovascular Pharmacology, Vol. 30, p. 261-272, exhibit H).

Claims 21 and 25 are directed to a compound identified by the method of claim 17, and a pharmaceutical composition comprising said compound and a pharmaceutical acceptable carrier.

Guth discloses a nonpeptidic molecule, BIBU52, that can inhibit the aggregation of human platelets in platelet-rich plasma induced by collagen, ADP, and a thrombin-receptor activating peptide. BIBU52 inhibits aggregation in plasma from rhesus and marmoset monkeys but not in rat plasma (e.g. abstract). The method by which the composition is obtained does not carry weight in 35 U.S.C. 102 rejection. The BIBU52 compound can inhibit platelet aggregation. The solution containing the BIBU52 compound is a pharmaceutical acceptable carrier. Thus, claims 21 and 25 are clearly anticipated by Guth.

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Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claims 17 and 20-24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Guth et al., 1997 (Journal of Cardiovascular Pharmacology, Vol. 30, p. 261-272, exhibit H) in view of Gayle et al., 1998 (The Journal Clinical Investigation, Vol. 10, No. 9, p. 1851-1859, exhibit G) and Choudhri et al., 1998 (J. Clin. Invest. Vol. 102, No. 7, p. 1301-1310, IDS-exhibit 8).

Guth discloses the use of three different animal models of recurrent arterial thrombus formation to test the efficacy of a compound, e.g. BIBU52 to inhibit ADP driven platelet aggregation in rhesus and marmoset monkeys. Guth does not disclose the use of CD39 or the compound does not increase the incidence of intracerebral hemorrhage.

Gayle discloses a recombinant soluble form of CD39 and demonstrate its antithrombotic activity *in vitro* by catabolizing ADP and resulting in the inhibition of platelet aggregation, and that it remained biologically active *in vivo* while circulating for prolonged periods of time (e.g. abstract, Figure 1, p. 1858).

Choudhri discloses testing the effects of a potent antiplatelet agent given both before and after the onset of middle cerebral arterial (MCA) occlusion in a murine model of stroke and

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shows a novel inhibitor of the glycoprotein IIb/IIIa receptor (SDZ GPI 562) exhibits a dose-dependent reduction of cerebral infarct volumes as well as improvement in postischemic cerebral blood flow. Choudhri also teaches GPI 562 causes a dose-dependent increase in tail vein bleeding time, but intracerebral hemorrhage (ICH) is not significantly increased at therapeutic doses (e.g. abstract).

It would have been obvious for one of ordinary skill in the art at the time of the invention to utilize an animal model of thrombosis to test for the effect of a potential therapeutic compound, such as soluble form of CD39 or GPI 562, on inhibiting ADP driven platelet aggregation and without increasing incidence of intracerebral hemorrhage. It would have been obvious for one of ordinary skill to compare the results of an animal model with and without the treatment of a test compound in order to determine the effects of said test compound.

One of ordinary skill at the time the invention was made would have been motivated to use the soluble CD39 as the test compound in the model set forth above because Gayle teaches it inhibits platelet aggregation *in vitro* by catabolizing ADP and that it remains biologically active *in vivo*, and Choudhri teaches antiplatelet agent, such as GPI 562, may cause increasing bleeding time in tail vein but ICH is not significantly increased at therapeutic doses, thus displaying the potential to inhibit platelet aggregation in an animal under thrombotic conditions and without increasing the incidence of ICH.

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14. Claims 25 and 26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Guth et al., 1997 (Journal of Cardiovascular Pharmacology, Vol. 30, p. 261-272, exhibit H) in view of Gayle et al., 1998 (The Journal Clinical Investigation, Vol. 10, No. 9, p. 1851-1859, exhibit G) and Choudhri et al., 1998 (J. Clin. Invest. Vol. 102, No. 7, p. 1301-1310, IDS-exhibit 8) as applied to claims 17 and 20-24 above, and further in view of Beaudoin et al., (US Patent No. 5,798,241).

The teachings of Guth, Gayle and Choudhri are as discussed above. Beaudoin teaches the use of a composition comprising mammalian ATP diphosphohydrolase with a pharmaceutically acceptable carrier to reduce platelet aggregation and thrombogenicity (claim 5, col. 9, lines 34-37).

It would have been obvious for one of ordinary skill in the art at the time of the invention to utilize a compound identified from an animal model of thrombosis which displays the activity of catabolizing ADP and without increasing incidence of intracerebral hemorrhage according to the collective teachings of Guth, Gayle and Choudhri, in a pharmaceutical composition as taught by Beaudoin in order to inhibit platelet aggregation in an animal under thrombotic conditions and without increasing the incidence of ICH.

Conclusion

Claims 2, 4-8 and 16-26 are rejected. Claims 1, 3 and 9-13 are in condition for allowance.

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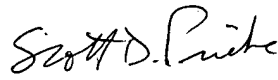
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.


SCOTT D. PRIEBE, Ph.D.
PRIMARY EXAMINER